



The Aldol Reaction

Introduction-

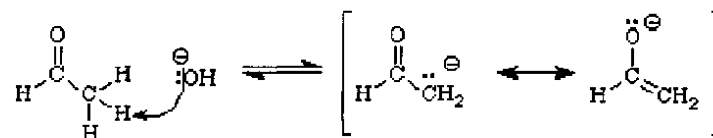
Near the end of the discussion of enolization there was an analysis of the reactivity of hydroxide ion towards the carbonyl carbon compared to the hydrogen α to the carbonyl carbon in acetaldehyde. That analysis concluded that addition to the carbonyl group was approximately 10,000 times more likely than abstraction of an α -hydrogen. But because addition of hydroxide ion to the carbonyl group is readily reversible, it is a non-productive reaction.

While the abstraction of an α -hydrogen is also a reversible reaction, the enolate ion that is formed has an alternative reaction pathway available to it- addition to the carbonyl carbon of another acetaldehyde molecule. This is called the aldol reaction. Figure 1 summarizes the process.

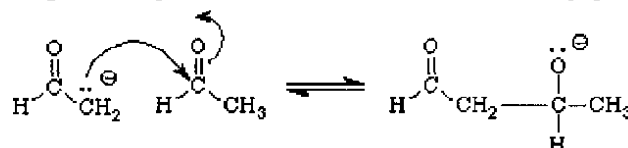
Figure 1

The Aldol Reaction of Acetaldehyde

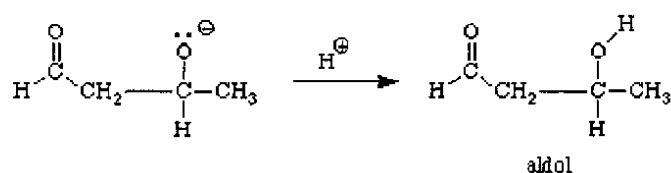
Step 1-Deprotonation of the α -carbon; generation of an enolate ion.



Step 2-Nucleophilic addition of the enolate ion to the carbonyl group.



Step 3-Protonation of the tetrahedral intermediate; formation of aldol.

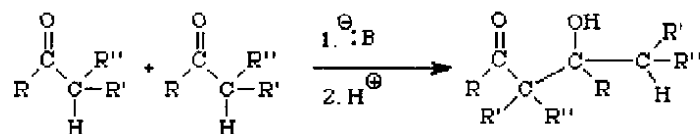


Note that the net effect of the aldol reaction is to add the "components of" one molecule of acetaldehyde to the carbonyl group of a second molecule of acetaldehyde, the "components of" acetaldehyde being H and HCOCH_2 .

The aldol reaction of two aldehydes is of limited synthetic utility. However, there are many "aldol-like" reactions which involve the essential features described in Figure 1. Figure 2 highlights these features.

Figure 2

General Features of the Aldol Reaction

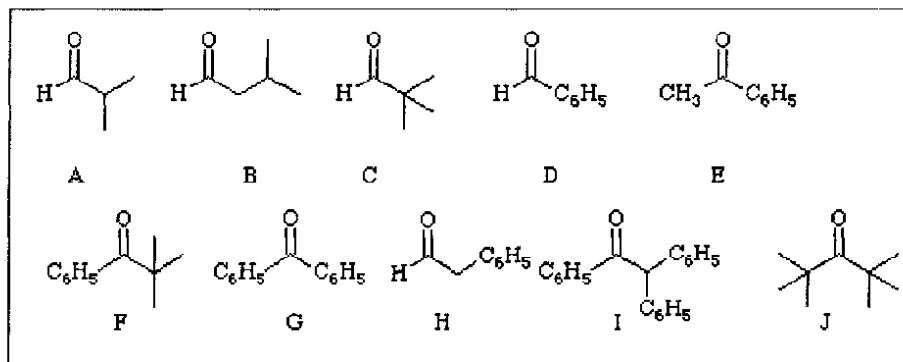


The aldol reaction requires an aldehyde or ketone that contains at least one α -hydrogen. The α -carbon becomes nucleophilic when it is deprotonated by a base. The carbonyl carbon is electrophilic. Coulomb's Law brings these two oppositely charged species together to form a C-C bond.

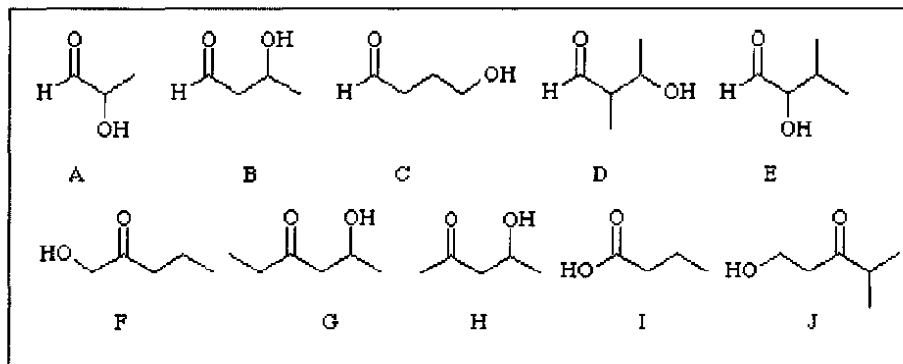
The R groups may be H, alkyl, or aryl. When the R groups in one molecule are different than those in the other, the reaction is called a crossed-aldol reaction. The ability to join different aldehydes and ketones together is what gives this process its synthetic value.

The word aldol is a common name for the product of the reaction shown in Figure 1. It is a type of compound called a β -hydroxyaldehyde. Generally the word aldol is used to refer to any β -hydroxyaldehyde or β -hydroxyketone.

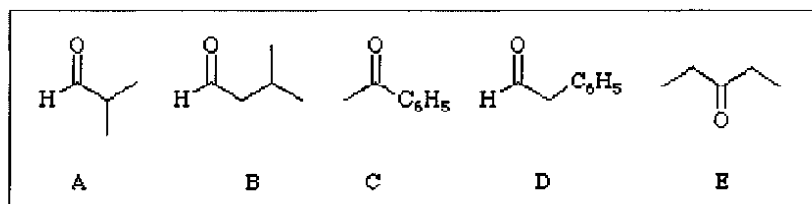
Exercise 1 Enter the letter of any compound that does not meet the structural requirements for the aldol condensation:



Exercise 2 Enter the letter of any β -hydroxyaldehyde or β -hydroxyketone into the text field:



Exercise 3 Draw the structure of the aldol that would be formed from the aldol condensation of each of the following aldehydes and ketones.



Like other alcohols, β -hydroxyaldehydes and β -hydroxyketones undergo dehydration to produce alkenes. In fact, it is difficult to isolate β -hydroxyaldehydes and β -hydroxyketones because they are very prone to dehydration.

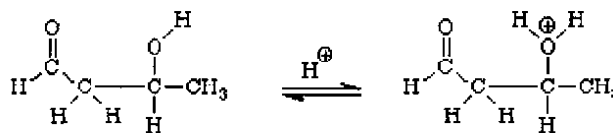
Dehydration of β -hydroxyaldehydes and β -hydroxyketones

In order to isolate the product shown in Figure 1, the reaction conditions must be mild; the temperature must be kept low and the amount of acid used to protonate the alkoxide ion intermediate must be carefully controlled. If too much acid is added, or if the temperature is too high, the aldol will dehydrate to form a **conjugated alkene** as demonstrated in Figure 3.

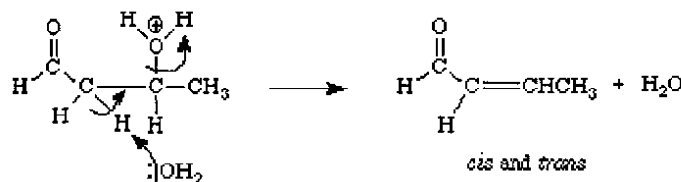
Figure 3

Dehydration of a β -hydroxyaldehyde

Step 1- Protonation of the OH group



Step 2- Abstraction of an H from C_{α} ; formation of a double bond.

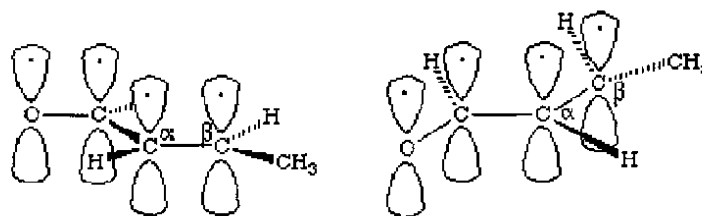


The conjugated alkene shown in Figure 3 is also called an α, β -unsaturated aldehyde. This means that the double bond is between the carbon atoms α and β to the carbonyl carbon. In this position the p orbitals of the double bond may interact with those of the carbonyl group to form

an extended, i.e. delocalized, pi system. The delocalization of the electrons in this pi system results in greater stabilization since the electrons experience greater nuclear attraction. Figure 4 offers two perspectives of the orbital geometry that affords this extra stabilization. The *trans* isomer was chosen arbitrarily.

Figure 4

Orbital Alignment in α, β -unsaturated Systems



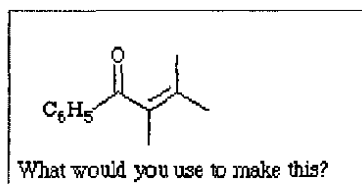
Exercise 4 Draw the structure of the α, β -unsaturated aldehyde or ketone that would be formed by dehydration of each of the aldol products you drew in Exercise 3.

Retrosynthetic Analysis

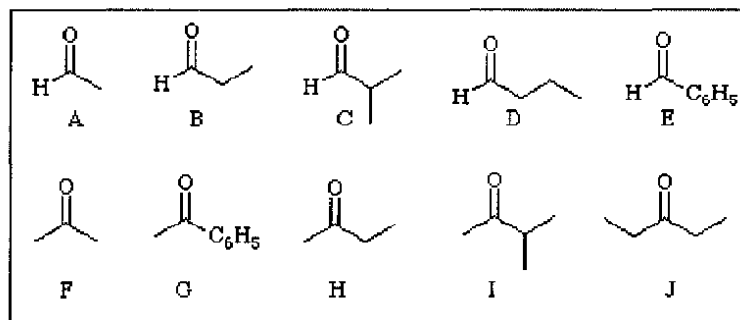
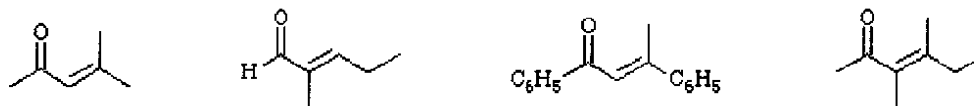
For synthetic organic chemists it's important to develop the ability to mentally "deconstruct" a target structure into simpler molecules from which that target may be made. The process of intellectual deconstruction is called retrosynthetic analysis. The focal point of such endeavors is inevitably the functional group(s) within the target molecule. In the case of α, β -unsaturated aldehydes or ketones the functional group of interest is the C-C double bond. Disconnecting these two carbons as animated in Figure 5 reveals the structures of the two components from which the target molecule was prepared.

Figure 5

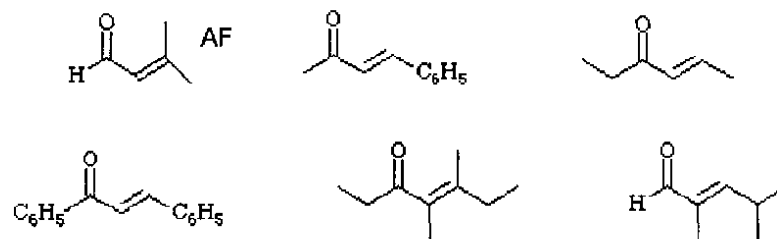
Take One Step Back



Exercise 5 Each of the following compounds was prepared by an aldol condensation followed by dehydration. In each case, select the structure of the starting material from the list of choices in the box below. Enter the appropriate letter into the text field.

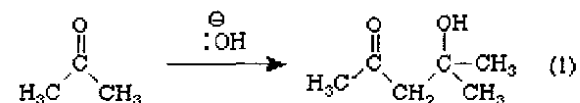


Exercise 6 Each of the following compounds was prepared by a crossed aldol condensation followed by dehydration. In each case, select the structures of the starting materials from the list of choices in the box above. Enter the letter of the compound that serves as the nucleophilic component followed by that of the electrophilic component. For example, the nucleophilic component used to prepare the first compound is A, while the electrophilic component is F.



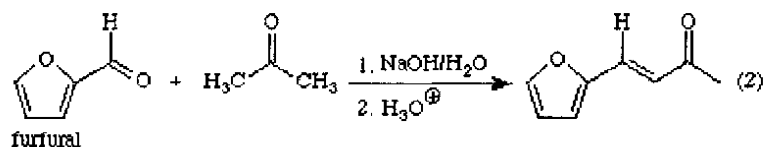
Examples

Treatment of acetone with base results in the aldol reaction shown in Equation 1.

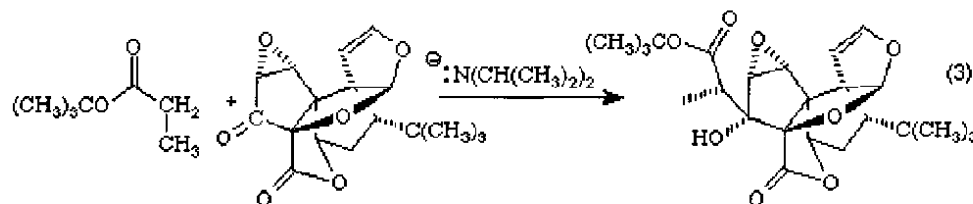


Experimentally reaction 1 is tricky to perform. However, if the product is separated from the reaction mixture as it is formed, it is possible to isolate the product in over 70% yield.

Acetone participates in a crossed-aldol reaction with furfural, an aldehyde produced from corn stalks, as described by Equation 2, where the carbon-carbon bond that is formed is highlighted in red.

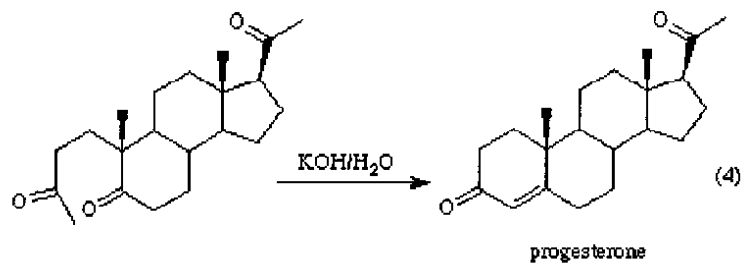


An amazing aldol-type reaction was involved in the total synthesis of ginkgolide B, one of the active components in extracts from the *Ginkgo biloba* tree. Equation 3 outlines this key step.



In this reaction the potentially nucleophilic carbon is α to the carbonyl group of an ester rather than a ketone or aldehyde. Lithium diisopropylamide (LDA) was used to deprotonate this carbon. The resulting enolate ion added to the carbonyl carbon of the complex pentacyclic ketone to form the C-C bond shown in red.

Equation 4 depicts an intramolecular crossed-aldol reaction that constituted the last step in a total synthesis of racemic progesterone. Even though the reaction conditions were very mild, the intermediate



β -hydroxyketone underwent spontaneous dehydration to produce the α, β -unsaturated ketone.

O=CHem Directory